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Research title: Single dose preoperative gabapentin use in minimally invasive hysterectomy for acute pain management

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Objectives:

The purpose of this study is to evaluate the efficacy of preoperative single dose gabapentin for subjects undergoing a minimally invasive hysterectomy in management of acute postoperative pain. The study will compare the effectiveness, and side effects of preoperative provision of three non-opioid oral medications (acetaminophen, celecoxib, and gabapentin) compared with acetaminophen and celecoxib alone (without gabapentin). As providing the least medication and lowest doses is consistent with best medical practices, we propose to assess whether provision of gabapentin does or does not provide significant reduction of post-operative pain above and beyond oral acetaminophen and celecoxib. We aim to assess efficacy with dual primary outcomes of reduction in 24 hour numeric analog scale (NAS) and reduction in 24 hour narcotic use.

Hypothesis:

We hypothesize a single preoperative dose of gabapentin 600 mg in addition to oral acetaminophen and celecoxib will meaningfully reduce the reported 24 hour postoperative NAS score by at least 35% and reduce the 24 hour narcotic use by at least 25% compared with preoperative acetaminophen and celecoxib alone. These effects are clinically meaningful, while conservatively lower than those found by Alayed et al (2014).

Background:

Multimodal postoperative analgesia after a hysterectomy has been mainly based on a combination of nonsteroidal anti-inflammatory drugs and opioids. However, adverse effects including nausea, vomiting, sedation, and pruritus may limit use of opioids (Dolin 2005). As the side effects are dose related, minimizing opioid exposure may significantly reduce these risks. Thus, there has been an interest in evaluating preemptive as well as post-operative administration of non-opioids. Additional regimens have been suggested to minimize opioid use and its associated adverse effects including injection of local anesthetics, epidural analgesia, and anticonvulsants, such as gabapentin or pregabalin (Tiippana 2007).

Gabapentin, a widely used anticonvulsant used for treatment of neuropathic pain, has recently been suggested to improve postoperative analgesia and reduce opioid requirements. Gabapentin is thought to modulate calcium channels on the presynaptic nociceptive neurons, which in turn modulate or inhibit the release of excitatory neurotransmitters from activated nociceptors (Schmidt et al 2013). In

addition to inhibiting pain transmission, gabapentin may exert an analgesic effect by activating descending inhibitory noradrenergic pathways (Schmidt et al. 2013).

Many studies have demonstrated the safety and efficacy of gabapentin for perioperative use in a variety of procedures across disciplines including thoracotomy, laparoscopic cholecystectomy, tonsillectomy, major orthopedic surgery, cesarean sections, and abdominal hysterectomy (Tiippana 2007). Several randomized trials have evaluated the effects of gabapentin administered preoperatively only as well as given pre- and postoperatively for hysterectomy. In a systematic review of 14 studies conducted between 2004 and 2013, with samples ranging from 40 to 200, Alayed et al. (2014) identified 8 trials in which gabapentin was administered only preoperatively to reduce pain associated with abdominal hysterectomy surgery. Analysis of those data clearly demonstrates that preemptive gabapentin reduced the postoperative visual analog scale (VAS) pain score by approximately 50% and postoperative use of morphine by approximately 37%. The incidence of pruritus and dry mouth in those receiving preemptive gabapentin appeared similar to those receiving placebo, however there was a higher rate of reported dizziness (not statistically significant) associated with gabapentin. In contrast, multiple postoperative doses of gabapentin in addition to the preoperative dose was found to have no significant effect on VAS scores at 24 hours, thus favoring a single preoperative dose.

Although initial results have been encouraging, uptake of gabapentin in routine clinical use remains limited due to mixed results and variability between gabapentin protocols, including dosing and duration. Christiana Care (CCHS) plans to implement the Enhanced Recovery After Surgery (ERAS) protocol which administers preoperative medications to reduce postoperative pain, including acetaminophen, celecoxib, dexamethasone, and gabapentin. Therefore the aim of this study is to assess the efficacy of a single dose of preoperative gabapentin to reduce acute postoperative pain in women undergoing a minimally invasive hysterectomy.

Study Design:

This is a double-blind, randomized controlled trial with a balanced 1:1 ratio evaluating the efficacy of single dose perioperative gabapentin above and beyond the effects of preoperative acetaminophen and celecoxib for women undergoing a hysterectomy via a minimally invasive approach.

Assuming a standard deviation equivalent to 50% of the average of both study groups (three medications including gabapentin compared to two medications excluding gabapentin), a sample of 51 women in each study group is needed using a two tailed test, $\alpha=0.05$, $1-\beta=90\%$. Assuming that the two primary outcomes are 80% correlated, a Bonferroni adjustment for multiple comparisons increases the sample size by 2 people per group. Therefore, in case of missing information and/or

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attenuation of effect should analyses controlled for confounding be necessary, the study plans to enroll 67 women per study group.

Study Participants:

Our study population will include all females undergoing a minimally invasive hysterectomy with surgeons operating within the Christiana Care at the Newark location only. Participants will be included if they are at least 18 years of age and undergoing hysterectomy for any indication via a minimally invasive approach – vaginal, laparoscopic, and/or robotic-assisted.

Participants will be excluded if they decline to participate, have a known history of liver or renal failure, a history of gastric bypass, gastroparesis, recent or current regular gabapentin use, or a hypersensitivity to gabapentin, acetaminophen, or celecoxib, or procedure is converted to laparotomy for any indication. Mini-laparotomy for specimen removal alone will not be excluded.

Consents will be requested from eligible subjects in the office setting at the time of scheduling their hysterectomy. Consenting participants will then be randomized into the experimental or control study group stratified by surgeon, to eliminate bias associated with provider experience. The preoperative medications will be administered 1-2 hours before surgery in the preoperative holding area. Both groups will continue to receive the standard preoperative care and medications per protocol at Christiana Care.

Study Protocol:

1. Procedure

Eligible participants will be approached and voluntary informed consent will be requested in the office setting at the time of their preoperative visit. Consenting subjects will then be randomized on the day of surgery to either the experimental or control group by the research coordinator. The study will use concealed envelop random allocation in which each group will be identified by an anonymous letter (X or Y); the identity of the study group allocation will be maintained in a locked file by the Chief Epidemiologist of the CCHS Department of Obstetrics and Gynecology, Nancy Sloan, and will not be revealed except to and if directed by the institutional. Randomization will be stratified by surgeon. While in the preoperative preparation and hold area, subjects will complete a survey to assess a baseline pain score. To support double-blind implementation, perioperative nurses will administer routine preoperative medications approximately 1-2 hours prior to surgery to ensure the study data collectors and data entry personnel are unaware of the study group allocation. Although the study does not have the funding to

support purchase of visually identical placebos, the study will support the double blind design by providing the same number of capsules to both study groups. Subjects in the control arm will receive acetaminophen 975 mg (three tablets of acetaminophen 325 mg) and celecoxib 400 mg (four capsules of celecoxib 100 mg) orally. Subjects in the study arm will receive gabapentin 600 mg (two capsules of gabapentin 300mg), acetaminophen 975 mg (three tablets of acetaminophen 325 mg), and celecoxib 400 mg (two capsules of celecoxib 200 mg) orally. Thus, both the experimental and control groups will receive three tablets and four capsules for perioperative oral medications to support the double blind design. Subjects will undergo their scheduled minimally invasive surgery as per routine by participating surgeons. Surgeons will be encouraged to administer 20 cc local 0.25% Marcaine distributed equally among all incision sites.

Postoperatively, subjects will continue to receive the standard of care as performed by the Christiana Care and the attending surgeon. Recovery and floor nurses will continue to manage patient care as routine, including assessing for patient pain immediately post operatively and at routine time points postoperatively until discharge, using either the verbal numerical rating scale or the Wong-Baker FACES pain rating scale. Subjects discharged prior to 24 hours will report their pain rating and narcotic medication use via telephone follow-up from a research coordinator. Up to 3 telephone calls will be made to maximize follow-up.

Subjects will also receive a phone call 2 weeks postoperatively to assess pain, postoperative narcotic use, and potential side effects.

Study Arms:

- **Gabapentin group:** Gabapentin 600 mg (two capsules of gabapentin 300 mg) , acetaminophen 975 mg (three tablets of acetaminophen 325 mg), Celecoxib 400 mg (two capsules of celecoxib 200 mg) = total 3 tablets, 4 capsules
- **Control group:** Acetaminophen 975 mg (three tablets of acetaminophen 325 mg), Celecoxib 400 mg (four capsules of celecoxib 100 mg) = total total 3 tablets, 4 capsules

Administration: Medication given 1-2 hours prior to surgery by preop RN

2. Confidentiality

Voluntary informed consent for study participation will be requested from all eligible subjects. To enable data collection, names and medical record numbers will be recorded on informed consent forms along with an assigned a study ID number to link these identifiers. To protect confidentiality, all data will be entered into an encrypted, password protected electronic file

using REDCap software. Hard copy informed consent forms will be maintained in locked files in the Principal Investigator's office and later destroyed in a manner compliant with CCHS data security. Extracted data from REDCap and data analysis files will be maintained on secure CCHS media/secure flash drive. When data collection is complete, all identifiers excepting the study ID number will be redacted from the data set to further protect confidentiality.

3. Subject Compensation

Participants will not be compensated for participating in this study.

Drugs or Devices:

Subjects will receive medications that are not investigational. The study medications have been preapproved for routine use in the enhanced recovery after surgery protocol at CCHS.

Data Collection Variables:

1. Primary Outcome Variables

- Narcotic use in the immediate 24 hour postoperative period is our co-primary outcome. Narcotic use postoperatively, both intravenous and oral, will be collected from subject charts and converted to standard equivalents of oral oxycodone using the equianalgesic table available at globalrph.com. Narcotic use after discharge will be assessed by telephone call and asking subjects to count pills remaining in prescribed medication bottles between 24 hours.
- Mean differences in pain scale rating from preoperative rating to rating 24 hours after surgery is our other co-primary outcome; ratings within a subject will be compared to other study participants in the control and study group. Pain scale assessment using a verbal numerical rating scale or the Wong-Baker FACES pain rating scale will be collected at four time points: prior to surgery, immediately on arrival to the PACU, arrival to the inpatient floor, and at 24 hours postoperatively.

2. Secondary Outcome Variables

- The study is not designed to test any hypotheses other than the primary outcomes. The study will, however, collect data on narcotic use over the entire 2 week postoperative period and assess pain at 2 weeks as well. In addition, the study will collect data on and analyze and describe side effects that may be contributed to gabapentin use. These variables include the presence or absence of postoperative nausea and vomiting, dizziness, somnolence, blurry vision, and tremulousness within the first 24 hours postoperatively. Presence of symptoms will be noted as either a documented complaint of the patient, postoperative administration of medication to treat

symptom (such as antiemetic administration while inpatient), documentation of symptom in the chart (such as emesis volume recorded), and/or subject confirms symptoms within the past 24 hours at the 24 hour postoperative phone survey.

Randomization criteria: Provider

Potential Confounding and Mediating Variables, Data Collection

- Age
- BMI
- PMH:
 - chronic pain syndromes (fibromyalgia, chronic pelvic pain, chronic back pain, neuropathy)
- PSH:
 - number of laparoscopic surgeries
 - number of open abdominal surgeries
 - total number of surgeries (including extra-abdominal surgeries)
- Procedure details:
 - indication for surgery
 - surgical approach (i.e. vaginal, lsc, robotic)
 - procedure other than hysterectomy
 - salpingectomy
 - oophorectomy
 - lysis of adhesion
 - sacrocolpopexy
 - perineorrhaphy
 - sacrospinous ligament fixation
 - sling (transobturator, TVT)
 - +/- mesh
 - lymphadenectomy (pelvic, aortic)
 - omentectomy
 - EBL
 - Operating time
 - use of local anesthetic at incision
 - method to remove specimen (i.e. minilaparotomy vs colpotomy vs power morcellation)
 - Attending surgeon
 - Date of surgery
- Surgical Complications:
 - Clavien-Dindo classification
 - infection
 - transfusion
 - wound separation
 - visceral injury
 - bowel

- bladder
- ureter
- blood vessel
- Patient survey (phone call)
 - 24 hours/2 weeks
 - pain scale
 - amount of oral pain narcotic used
 - experienced following symptoms
 - nausea
 - vomiting
 - dizziness
 - ataxia
 - tiredness/somnolence
 - blurred vision
- Pain rating postop: define on arrival to PACU (= 0 hours)
 - Arrival to PACU
 - Arrival to floor
 - 24 hours postop
 - 2 weeks postop

Method of Analysis:

The study data will be entered into an MS Access database that will be maintained on the protected CCHS computer system and approved encrypted thumb drives. Descriptive statistics using chi-square for categorical and Student's t-tests for continuous variables, with Fisher's continuity correction for analyses with fewer than 5 subjects in any cell will be reported. Linear (for continuous outcome) and logistic (for categorical variables) regression analyses will be conducted to adjust for confounding factors and assess mediation of effect (for example, associated with surgical complications).

Risks/Benefits:

The Christiana Care Institutional Review Board will review this study protocol. The study will be registered with ClinicalTrials.gov prior to enrollment of its first patient. Voluntary informed consent for study participation will be requested of all eligible women undergoing a minimally invasive hysterectomy for any indication. This study carries a small risk regarding breach of confidentiality, as protected health information will be collected. However information will be kept coded and secure in accordance with CCHS data security measures and REDCap software.

There is a potential risk for side effects from gabapentin administration including temporary dizziness/drowsiness, fatigue, loss of balance, blurry vision, tremulousness, swelling, nausea, vomiting, diarrhea, and allergic reaction, however these side effects are rare. Risks of side effects from gabapentin are also minimal as

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the study will only administer a single dose. Potential benefits include improved postoperative pain management, less narcotic use, and decreased postoperative nausea and vomiting.

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